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Isolated hematuria in children: Indications for a renal biopsy

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Isolated hematuria in children: Indications for a renal biopsy. Previous reviews of hematuria in children and adolescents have included patients with proteinuria and other renal functional abnormalities such as hypertension and reduced GFR. We report the clinico-pathological correlations in 76 pediatric patients, aged 3 to 19 years, who underwent a renal biopsy because of isolated hematuria during the 10-year period, 1972 to 1981. All specimens were examined by light and electron microscopy and immunofluorescence techniques. The overall prevalence of abnormal renal histology was 56%. The vast majority (41 of 43) of the abnormal biopsy specimens could be classified into four distinct histological categories: *(1)* Alport syndrome ($N = 9$); *(2)* IgA nephropathy ($N = 8$); *(3)* thinning of the glomerular basement membrane ($N = 17$); *(4)* vascular C_3 staining ($N = 7$). The children were divided into three clinical subgroups *(1)* isolated microscopic hematuria (IMH), $N = 42$; *(2)* IMH plus a family history of hematuria in a first degree relative, $N = 15$; and *(3)* IMH plus at least one episode of gross hematuria, $N = 19$. A significant graded increase in the likelihood of obtaining an abnormal renal biopsy was demonstrated ($X^2 = 10$, $P < 0.007$) from groups one to three. Sex, age at onset, or duration of hematuria were not associated with an increased proportion of histopathologic abnormalities. These findings indicate that the yield of a renal biopsy in children with isolated hematuria can be predicted accurately from specific clinical characteristics.

Hematurie isolee de l'enfant: Indication de la biopsie renale. Des revues antérieures sur les hématuries de les enfants et de les adolescents incluaient les malades ayant une protéinurie et d'autres anomalies fonctionnelles rénales comme une hypertension et une diminution de GFR. Nous rapportons des corrélations clinico-pathologiques chez 76 malades pédiatriques, âgés de 3 à 19 ans, qui ont subi une biopsie rénale en raison d'une hématurie pendant une période de 10 ans, 1972 à 1981. Tous les échantillons ont été examinés en microscopie optique et électronique, et avec des techniques d'immunofluorescence. La prévalence globale d'une histologie rénale anormale était de 56%. La grande majorité (41 du 43) des échantillons biopsies anormales pouvait être classée en quatre catégories histologiquement distinctes: *(1)* Syndrome d'Alport ($N = 9$); *(2)* néphropathie à IgA ($N = 8$); *(3)* amincissement de la membrane basale glomérulaire ($N = 17$); et *(4)* coloration vasculaire avec C3 ($N = 7$). Les enfants ont été divisés en trois sous-groupes cliniques: *(1)* hématurie microscopique isolée (IMH), $N = 42$; *(2)* IMH plus une histoire familiale d'hématurie chez un parent du premier degré, $N = 15$; *(3)* IMH plus au moins un épisode d'hématurie macroscopique, $N = 19$. Une augmentation progressive significative de la possibilité d'obtenir une biopsie rénale anormale a été démontrée ($X^2 = 10$, $P <$ 0,007) des groupes un à trois. Le sexe, l'âge lors de la découverte, ou la durée de l'hématurie n'étaient pas associés à une proportion augmentée d'anomalies histopathologiques. Ces données indiquent que le résultat d'une biopsie rénale chez des enfants avec une hématurie isolée peut être prédit de façon précise à partir de caractéristiques cliniques spécifiques.

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The point prevalence of asymptomatic hematuria in the pediatric population ranges from 0.5 to 2.0% according to recent screening surveys of school age children [1, 2]. Despite the frequency of its detection, considerable disagreement persists about the proper nature and extent of the diagnostic work-up that is warranted for this solitary urinary abnormality [3]. In particular, the role of a renal biopsy in the evaluation of the child with hematuria remains controversial. Previous reviews of children with hematuria failed to correlate renal biopsy findings with the presence or absence of gross hematuria, positive family histories of hematuria, or concomitant proteinuria [2, 4–9].

The present retrospective review of children with isolated hematuria who underwent renal biopsy at a referral center was undertaken to provide the following information: *(1)* the overall prevalence of abnormal renal histology among these patients; *(2)* the identification of those clinical characteristics that may enable recognition of children with an increased likelihood of having abnormal renal histology; *(3)* a description of two histologic patterns observed in children with hematuria, thinning of the glomerular basement membrane (GBM) and vascular C_3 staining, that have not been associated with a clinically defined nosological entity; and *(4)* assessment of the clinical course of children with isolated microscopic hematuria.

Methods

The clinical records and pathology reports of all children with hematuria who underwent a renal biopsy at the Hospital of the Albert Einstein College of Medicine, Bronx, New York, in the years 1972 to 1981 were reviewed. During this period, the prevailing practice was to perform a renal biopsy in any child with hematuria lasting longer than 6 months. Patients were included in the study only if an adequate tissue specimen was available for examination by light and electron microscopy and immunofluorescence techniques. The children were well except for the finding of hematuria and had no signs or symptoms suggestive of a systemic disease. They had no clinical or radiographic signs of nephrolithiasis at the time of renal biopsy. Routine prebiopsy laboratory evaluation included a urine culture, serum creatinine concentration with an estimated GFR [10], sickle cell screening, measurement of serum C_3 concentration (radial immunodiffusion, Calbiochem-Behring Corp., La Jolla, California), and an intravenous pyelogram at the time of the biopsy. Assessment of urinary calcium excretion and audiograms were not routinely performed. The initial detection of microscopic hematuria by a semiquantitative testing method

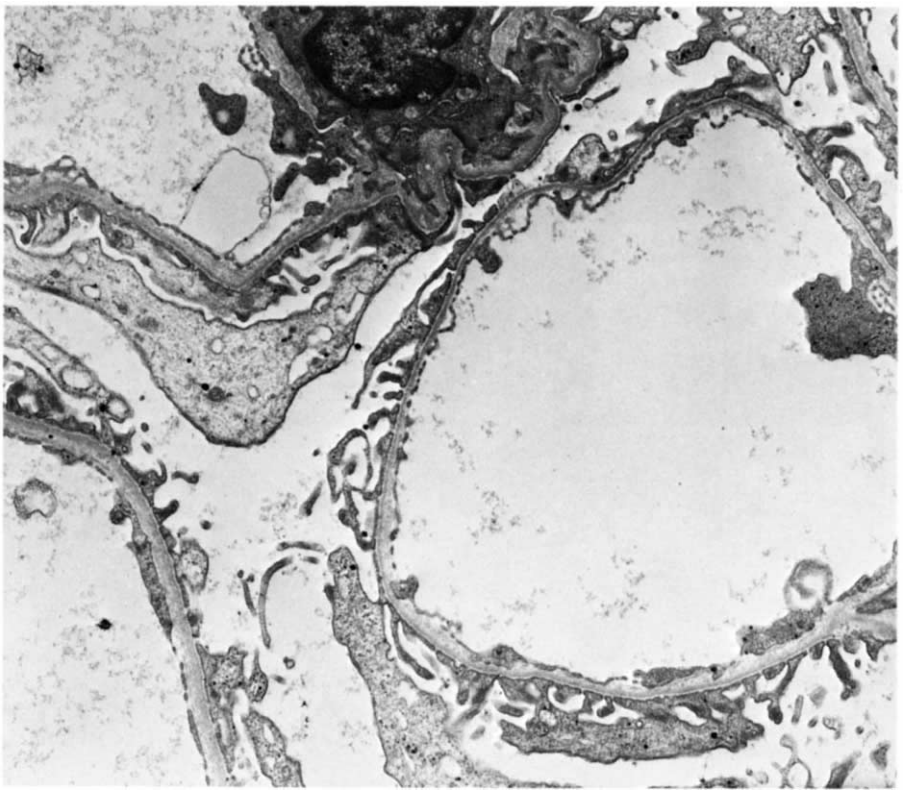

Fig. 1. *Electron micrograph showing thinning of the GBM.* The capillary loop on the *right side* of the figure is affected while those on the *left* are of normal thickness. (×5400)

(for example, Hemastix, Ames) was always confirmed by the Addis count technique. Hematuria was defined as a RBC excretory rate exceeding 240,000 per 12 hr in an overnight urine collection on at least two occasions over a 6-month period. In fact, every child who underwent a renal biopsy had at least one Addis count demonstrating more than 500,000 RBC in a 12-hr collection period. No distinction was made between patients who had persistent abnormal urine testing results and those who demonstrated only intermittent hematuria. Gross hematuria was defined by history or visual inspection of a urine specimen. The family history for hematuria was considered positive only if it involved a first degree relative (parent or sibling). The documentation of a positive family history was confirmed in one half of the cases by quantitative urine testing of affected family members.

Proteinuria, defined in accordance with the International Study of Kidney Diseases in Children as greater than 4 mg/M^2/hr [11], was a criterion for exclusion from the study group. An estimated GFR below 80 ml/min/1.73 M^2, a blood pressure exceeding the 95th percentile for age and sex [12], a serum C_3 level below 50 mg/dl, or an anatomic abnormality of the urinary tract also served to exclude the affected patient from further consideration in this review.

The renal biopsies were performed percutaneously under fluoroscopic or ultrasound guidance. Following fixation in solution (Dubosq-Brazil), paraffin sections were cut at 4-μM thickness and stained with hematoxylin-eosin, Masson trichrome, periodic acid Schiff and Jones' silver methenamine methods. Frozen sections were cut and stained with fluorescein isothiocyanate-coupled antisera to IgG, IgA, IgM, C_3, C_4, and fibrinogen. The tissue samples for electron microscopy were fixed in glutaraldehyde, postfixed in osmium tetroxide and embedded in Epon 812. Ultrathin sections were cut and stained with uranyl acetate and lead citrate. The renal biopsy specimens were interpreted by a single pathologist who was aware of the clinical status of each patient.

IgA nephropathy (Berger disease) was defined as bright staining with anti-IgA antisera in glomerular mesangia. Alport syndrome was diagnosed on the basis of characteristic electron microscopic abnormalities of the GBM, namely splitting and lamination of the lamina densa with accumulation of small dense particles in lucent areas between split layers [13–16]. The thickness of the GBM was measured from the outer aspect of the endothelial cell to the inner aspect of the visceral epithelial cell, using a calibrated electron microscope. The accuracy of the calibration was verified by comparison with a standard reference grid photographed at equal magnification (×20,000). The measurements were made at a site along the peripheral glomerular capillary loop where both cell membranes could be resolved to insure that the determinations were uniform and represented ideal cross sections. The width of the lamina densa was also recorded. Measurements to establish the diagnosis of GBM thinning were made only on those biopsy specimens in which the thickness of a capillary loop appeared attenuated along its entire extent. Thinning of the GBM was defined as an endothelial-to-epithelial thickness less than 1500 Å and a lamina densa width less than 1,000 Å at any location along its length (Fig. 1). The presence of vascular C_3 was defined by bright staining of arterioles in the renal interstitium with anti-complement antisera (Fig. 2).

Followup information on the children with isolated microscopic hematuria, Alport syndrome, and IgA nephropathy

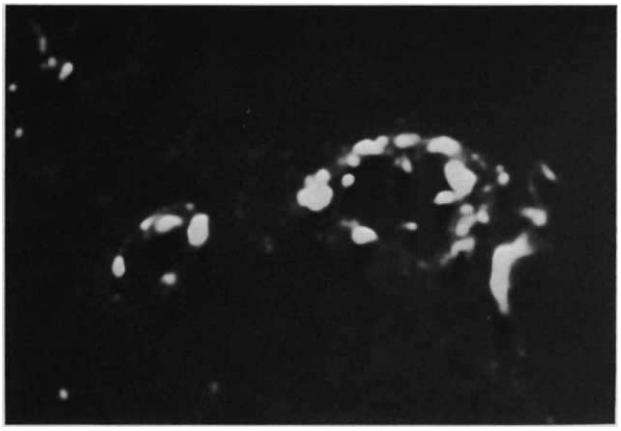

Fig. 2. *Immunofluorescence photomicrograph showing the presence of vascular C_3.* The arterioles in the interstitium contain granular deposits. (×240)

consisted of the results of the most recent measurement of the child's BP, urinalysis, and tests of renal function.

The results were analyzed utilizing the χ^2 test or, where appropriate, Fisher's exact test. The student's t test was used to compare the difference between the means of unpaired samples. The results were considered statistically significant if $P < 0.05$.

Results

Biopsy specimens were taken from a total of 76 children with isolated hematuria during the 10-year period (1972 to 1981). Their ages were uniformly distributed between 3 and 19 years with an equal number of male and female patients. Eight adolescents were older than 15 years at the time of biopsy; however, in seven instances the hematuria was detected prior to 15 years of age. The duration of hematuria from the time of detection to the date of biopsy ranged from 6 months to 14 years with a mean interval of 32.4 months. Each biopsy specimen contained at least 15 glomeruli. The only complication of the procedure was a single instance of an AV fistula that required embolization.

The children were divided into the following three clinical categories based on historical data obtained prior to the biopsy (Table 1): *(1)* isolated microscopic hematuria (IMH), $N = 42$; *(2)* isolated microscopic hematuria plus a family history of hematuria in a first degree relative (IMH and F), $N = 15$; and *(3)* microscopic hematuria and episodes of gross hematuria (IMH and GH), $N = 19$. Seven patients in this third group had only a single episode while 12 patients had recurrent episodes of macroscopic hematuria. The second and third categories were not mutually exclusive; in fact, among the 19 children with GH were four patients who also had a family history of hematuria.

The pathologic diagnoses made in the study population are listed in Table 2. Thirty-three biopsy specimens (44%) were considered completely normal after examination by light and electron microscopy and immunofluorescence. Among the 43 children with abnormal renal histology, GBM characteristics of Alport syndrome were detected in nine biopsy specimens (12% of total sample), IgA nephropathy (Berger disease) in eight (11%), and seven children (9%) had moderate to marked immunofluorescence staining of arterioles in the interstitium for

Table 1. Isolated hematuria

Clinical categories	*N*	*%*
Isolated microscopic hematuria (IMH)	42	55
Isolated microscopic hematuria plus a family history of hematuria (IMH and F)	15	20
Microscopic hematuria plus at least a single episode of gross hematuria (IMH and GH)[a]	19	25
Total	*76*	*100*

[a] Four patients in this category also had a positive family history.

Table 2. Isolated hematuria

Renal biopsy results	*N*	% Total biopsies	% Abnormal biopsies
Normal	33	44	—
Alport syndrome	9	12	21
IgA nephropathy	8	11	19
Thinning of the GBM	17	22	40
Vascular C_3 staining	7	9	16
Focal glomerulonephritis	1	1	2
Tubulointerstitial nephritis	1	1	2
Total	*76*	*100*	*100*

C_3. In addition, there were 17 children (22%) with thinning of the GBM. The total GBM and lamina densa widths in these children were 1233 ± 51 Å (mean ± SE) and 682 ± 31 Å, respectively. Both measurements were significantly less ($P < 0.00001$) than the values obtained in children with a normal GBM, namely, 1863 ± 31 Å and 1402 ± 40 Å. Finally, two biopsy specimens were abnormal but could not be placed into these diagnostic categories; one revealed a mild focal glomerulonephritis with increased mesangial matrix and hypercellularity, the other an area of tubulo-interstitial nephritis.

Analysis of the data revealed that sex, age at detection of the hematuria, and duration of the abnormality were not associated with an increased likelihood of abnormal histology. However, when the children were divided into the three clinical categories defined above, there was a highly significant graded increase in the proportion of abnormal biopsy results among children with either a family history of hematuria (64%) or the occurrence of gross hematuria (79%) compared to children with IMH (40%) ($X^2 = 10$, $P < 0.007$) (Table 3). The groups with a positive family history of hematuria or any episodes of gross hematuria had a higher incidence of Alport syndrome ($P < 0.01$) and IgA nephropathy ($P < 0.002$). However, the distribution of thinning of the GBM and vascular C_3 staining among the three clinical categories did not differ from that of the population of children with hematuria as a whole (Table 4). Of the four children who demonstrated both a positive family history of hematuria and at least a single episode of gross hematuria, three had GBM findings of Alport syndrome and one had IgA nephropathy.

Among the 40 patients with IMH whose renal biopsy specimen was either entirely normal ($N = 25$), demonstrated thinning of the GBM ($N = 10$), or vascular C_3 staining ($N = 5$), followup data were available for 26 (65%) children. The duration of followup dating from the detection of hematuria ranged from 13

Table 3. Isolated hematuria: Renal biopsy results by clinical categories

	IMH[a,b]		IMH and F[a]		IMH and GH[b]		Total	
	N	%	*N*	%	*N*	%	*N*	%
Normal	25	60	4	36	4	21	33	44
Abnormal	17	40	11	64	15	79	43	56
Total	*42*	*100*	*15*	*100*	*19*	*100*	*76*	*100*

[a] IMH vs. IMH and F: $X^2 = 4.8$, $P < 0.03$.
[b] IMH vs. IMH and GH: $X^2 = 7.8$, $P < 0.005$.

Table 4. Isolated hematuria: Abnormal renal biopsy results by clinical categories

	IMH		IMH and F		IMH and GH	
	N	%	*N*	%	*N*	%
Alport syndrome	1	6	2	18	6	40
IgA nephropathy	1	6	0	0	7	47
Thinning GBM	10	59	5	46	2	13
Vascular C_3	5	29	2	18	0	0
FGN	0	0	1	9	0	0
Tubulointerstitial nephritis	0	0	1	9	0	0
Total	*17*	*100*	*11*	*100*	*15*	*100*

to 90 months with a mean interval of 42.1 months. Twenty-two (85%) of the children still had IMH, but none had manifested any episodes of gross hematuria. All of the patients had yearly evaluations that included measurement of BP, urinary protein excretion, and serum creatinine concentration. No abnormalities were detected in any of these three variables during the followup period. Followup information was available for six of the nine children with Alport syndrome, the mean interval being 60 months. Hematuria persisted in all six patients. Although four of six patients had developed significant proteinuria, none manifested any evidence of diminished renal function. Among the eight children with IgA nephropathy, followup data was obtained in six instances for a mean duration of 72 months. All patients continued to have microscopic hematuria with intermittent episodes of gross hematuria. However, no child has developed proteinuria or signs of decreased renal function.

Discussion

The indications for performing a renal biopsy and the yield and type of abnormal results that can be expected in a child with isolated hematuria cannot be ascertained from the literature. Previous clinico-pathologic correlations in children with hematuria have included patients with proteinuria, hypertension, or an abnormal GFR. Moreover, many of the older series were compiled at a time when immunofluorescence and electron microscopy were not standard procedures. We avoided these confounding variables by examining the renal histopathology in a large group of otherwise well children with isolated hematuria. All biopsy specimens were examined by light and electron microscopy and immunofluorescence techniques. Analysis of this homogenous sample of patients has enabled us to identify clinical features associated with an increased likelihood of abnormal renal histology, and thus formulate indications for performing a renal biopsy in children with hematuria.

Four histological lesions, Alport syndrome, IgA nephropathy, thinning of the GBM and vascular C_3 staining, accounted for 95% of the abnormal renal biopsy specimens. IgA nephropathy and Alport syndrome are established clinical entities and are well recognized causes of isolated hematuria. IgA nephropathy may present as IMH, but it is usually characterized by recurrent, brief, and self-limited episodes of gross hematuria occurring in association with upper respiratory infections [17, 18]. Although the prognosis for children with IgA nephropathy is generally deemed to be favorable [17], pediatric patients have been described who developed progressive glomerular sclerosis and renal insufficiency [18–21]. Alport syndrome is the most common variety of hereditary nephritis. It is characterized by a positive family history of renal disease, sensorineural deafness, ocular abnormalities, and progressive renal failure although all four features need not be present to make a diagnosis [22]. Isolated hematuria in early childhood is often the first sign of disease, with the subsequent appearance of proteinuria in later years. Hearing loss may not develop until the second decade of life. Progressive deterioration in renal function is more common in males, although the interval until endstage renal disease supervenes varies from family to family [16, 22]. In contrast to Alport syndrome and IgA nephropathy, thinning of the GBM [23–25] and vascular C_3 staining are primarily histopathologic diagnoses. At present, they have no distinctive clinical presentation, course, or prognosis.

Thus, from the long list of glomerulopathies that are commonly enumerated in the differential diagnosis of hematuria, in our series of children and adolescents with this isolated urinary abnormality, we found that only two clinical entities occurred with any significant frequency. The early diagnosis of Alport syndrome is of value to provide genetic counseling to affected families. However, the exact mode of inheritance of the syndrome is still controversial and may vary from kindred to kindred [22]. In addition, no therapy presently available can effectively halt the progression to renal failure. Knowledge that a patient has IgA nephropathy is helpful in explaining the cause of and alleviating the anxiety provoked by recurrent episodes of gross hematuria. However, as with Alport syndrome, no form of therapy is currently available that can shorten or modify the natural history of this disease syndrome [17, 18].

The thinning of the GBM that we observed has been described previously in children and adults [23–26]. Our diagnostic criteria for this lesion were considerably more strict that those of previous reports in which a lamina densa width between 1,000 to 2,000 Å was considered abnormal [23, 24]. The GBM thickness is known to increase with age from a normal mean width of 1100 Å in "young children" to a mean value of 2700 Å in "older children and adults" [27]. However, a young age cannot be invoked to explain the attenuated GBM thickness in the 17 affected children since their mean age (9.3 years) was not different from that of the entire sample population (9.8 years). While some authors consider this finding specific for benign familial hematuria [23, 24], it is also included in the broad spectrum of GBM abnormalities that have been described in association with Alport syndrome [22, 25, 26, 28].

In fact, some investigators consider thinning of the GBM a forme fruste of Alport syndome [25]. Therefore, since attenuation of the GBM has been described in all forms of familial hematuria, its presence does not enable one to discriminate between benign familial hematuria and progressive hereditary nephritis [25, 29]. The family history and clinical course of other affected family members appeared to be the only reliable prognostic indicators of an individual patient's outcome [29]. In our series, none of the 17 children with thinning of the GBM had sensorineural hearing loss. Moreover, there was not an increased frequency of a positive family history of hematuria among these children compared to the total sample population. The prognosis for these children will remain unknown until a large cohort is prospectively followed. Similarly, the clinical outcome for the children with vascular C_3 immunofluorescence staining is unclear. This lesion has been documented in a recent clinico-pathologic study of isolated proteinuria in school age children [30] and in children with IgA nephropathy [18]. It has never been reported in children with isolated hematuria. Our patients with this lesion had no clinical or laboratory findings that distinguished them from the other children with isolated hematuria. This histologic abnormality cannot presently be considered a definite disease entity with long-term implications.

When the population of children with hematuria was divided into distinct clinical categories, characteristics were identified which were associated with an increased frequency of abnormal renal histology. These features were selected because they were likely to correlate with the occurrence of renal histopathology and are readily available to the primary care physician prior to referral for renal biopsy. Among the 42 children who had only IMH, 40% of their biopsy specimens were not entirely normal; however, 88% of the abnormalities noted were either thinning of the GBM or vascular C_3 staining, lesions of unknown, but doubtful clinical significance (Table 4). The benign renal biopsy findings among the children with isolated microscopic hematuria agree with those of Vehaskari et al [2], in which one possible case of Alport syndrome and two cases of IgA nephropathy were detected among 28 children with IMH. The presence of a family history of hematuria in a first degree relative increased the yield of an abnormality from 40 to 64%, and the presence of gross hematuria further enhanced the likelihood of an abnormal renal histology to 79% (Table 3). Moreover, clinically relevant entities, namely Alport syndrome, IgA nephropathy, comprised 58% (15 of 26) of the abnormal biopsy results in these latter two clinical categories (Table 4). The combination of both risk factors, namely a positive family history and the occurrence of gross hematuria, was uniformly associated with an abnormal renal biopsy specimen. No other factor examined, including sex, age, or duration of hematuria, had any predictive value for abnormal histology. Knowledge of these clinical features should enable the practitioner to predict the likelihood of obtaining an abnormal renal biopsy result in a child with hematuria.

In conclusion, based on these findings and our interpretation of the biopsy results, we would make the following recommendations with regard to a child who has had isolated hematuria lasting longer than 6 months. If there is a positive family history of hematuria in a first degree relative or the patient has had at least one episode of gross hematuria, then a renal biopsy is indicated. According to our findings, nearly 75% of such biopsy specimens will be abnormal and clinically important diagnoses, namely IgA nephropathy and Alport syndrome, will be made in the majority (60%) of cases. However, for the child who has only IMH, a renal biopsy is not a useful diagnostic procedure since it can nearly always be expected to reveal either normal morphology or nonspecific alterations of unknown clinical relevance. Until the implications of GBM thinning and vascular C_3 staining become clarified in multicenter prospective studies, the risk of routinely subjecting such children to a renal biopsy may outweigh any gain to be accrued from the early knowledge of a histological abnormality. This conclusion is supported by our followup information that failed to reveal any new urinary abnormality or deterioration in renal function among these children. Careful followup examinations for proteinuria, hypertension or decrease in GFR are warranted and any new finding should prompt re-evaluation of the patient and the need for a renal biopsy.

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